REMARKS

Claims 1-23, 36, 44, 45, 85-92 and 96-99 constitute the pending claims in the present application. Claims 1, 5, 15, 16, 86, 87, 96 and 99 have been amended. Claims 17, 20, 21, 91 and 92 have been withdrawn from consideration. The claim amendments and additions are fully supported by the specification. No new matter has been introduced.

In particular, exemplary support for the amendments to claim 1, 96 and 99 can be found, for example, at page 4, lines 26-32, page 13, lines 1-17, etc. Claims 5, 15, 16, 86 and 87 have been amended to correct typographical errors.

Amendment or cancellation of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application and do not, and are not intended to, narrow the claims in any way. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim Rejections Under 35 U.S.C. §103

Claims 1-16, 18-19, 22-23, 36, 44-45, 85-90 and 96-99 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Barbas et al. (a) (WO 94/18221) and further in view of Dower et al. (WO 96/40750) and Barbas et al. (b) (PNAS 92: 2529-2533 (1995)) and as evidenced by Helms et al. (Protein Science 4: 2073-2081 (1995)). Applicants respectfully note that the rejection under 35 U.S.C. §103(a) over Barbas et al. (a), Dower, Barbas et al. (b) and Helms et al. was withdrawn in the Office Action dated February 14, 2005 (see page 3 of Office Action dated February 14, 2005) in view of new grounds of rejection under 35 U.S.C. §103(a) over Barbas et al. (a), Dower, Barbas et al. (b) and Kini et al. (FEBS Letters 375: 15-17 (1995)). Since the current Office Action relies on the Kini et al. reference and does not rely on the Helms et al. reference, Applicants will address the rejection on the basis of the references actually relied on, e.g., Barbas et al. (a), Dower, Barbas et al. (b), and Kini et al. Clarification is respectfully requested if the Examiner intended to rely on the Helms et al. reference. Applicants respectfully traverse this rejection.

The Examiner relies on Barbas (a) for allegedly disclosing replacement of CDRs in a heavy or light chain antibody or Fab fragment with biologically active peptides and Barbas (b) is relied on for use of an anti-tetanus toxoid antibody for CDR3 replacement. Dower is relied on for disclosure of TPO mimetics. Finally, Kini is relied on for allegedly disclosing the incorporation of proline brackets within a peptide sequence and that such proline brackets introduce no undue strain along the backbones and thus allow flexibility of the interaction sites. The Examiner states that it would have been obvious to incorporate TPO peptides into a CDR region of an antibody because Barbas (a) teaches that human antibodies have therapeutic benefits and Dower teaches that TPO peptides can be used for therapy. Furthermore, the Examiner states since Kini et al. teaches a novel approach to the design of potent bioactive peptides by incorporation of proline brackets and that EPO and TPO mimetics are biologically active peptides, it would have been obvious to have used the biologically active peptides as modified, via incorporation of proline residues, by the teachings of Kini et al. in place of CDRs within a heavy or light chain as taught by Barbas et al. (a). See Office Action at pages 3-7.

Applicants respectfully disagree and note that pursuant to MPEP 2142, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

With respect to claims 1-16, 18-19, 22-23, 36, 90, and 96-99, Applicants respectfully submit that the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein at least a portion of a CDR region is replaced with an agonist peptide (such as an EPO or TPO mimetic) that binds to and agonizes a receptor (such as an EPO or TPO receptor) as claimed in the instant application. In particular, Barbas (a) states that the antibodies described in the application "are particularly well suited for *in vivo* use as a therapeutic reagent for blocking or inhibiting the function of the target molecule which the antibody binds" (see e.g., page 75, lines 29-34). Barbas (a) further provides specific examples of methods for inhibiting platelet gpIIb/IIIa

function, methods for inhibiting HIV gp120-mediated events, and methods for inhibiting vitronectin receptor-mediated events (see e.g., pages 78-83) using the CDR replaced antibodies. Accordingly, Barbas (a) teaches methods for designing and using CDR replaced antibody molecules that *inhibit* or *antagonize* receptor function, e.g., by binding to the receptor and interfering with ligand binding. There is no teaching or suggestion in Barbas (a) that CDR replaced antibodies could be used to stimulate or agonize receptor function and/or receptor mediated events.

The additional references cited by the Examiner fail to make up for the deficiencies of Barbas (a). In particular, Barbas (b) discloses anti-tetanus toxoid Fab molecules that are CDR replaced and bind to DNA. Such antibodies do not even bind to a receptor let alone suggest that such antibodies could be used to agonize receptor activity. Furthermore, there would be no motivation for one of skill in the art to combine the teachings of Barbas (a) with the teachings of Dower. Specifically, Barbas (a) teaches methods for designing and using CDR replaced antibodies that *antagonize* receptor function while Dower discloses TPO *agonist* peptides. One of skill in the art would not be motivated to incorporate peptides whose therapeutic value comes from the ability to stimulate receptor activity into a system useful for designing antibodies that inhibit receptor function. Therefore, one of ordinary skill in the art would not be motivated to incorporate agonist peptides, such as the TPO peptides of Dower, into the CDR replaced antibodies of Barbas (a) or (b). Furthermore, none of the references provide a suggestion that such a combination should be made nor that such a combination would have any therapeutic utility.

Finally, Kini et al. fails to make up for the deficiencies of Barbas (a) and (b) and Dower. Kini merely proposes that proline residues flanking protein-protein interaction sites perform a structural role in enhancing their interaction. However, Kini fails to teach or suggest that an agonist peptide (such as EPO or TPO) should be incorporated into the CDR region of an immunoglobulin or a fragment thereof.

Accordingly, none of the references cited by the Examiner, taken alone or in any combination teach or suggest the CDR replaced antibodies as claimed in the instant application. No combination of the cited references teaches inserting agonist peptides into an immunoglobulin wherein the resulting immunoglobulin has an agonistic activity. Rather, the cited references merely teach immunoglobulins which bind and block receptors and therefore are antagonists. In particular, the references relied on by the Examiner merely teach CDR replaced inhibitory antibodies and TPO peptides that are useful as agonists. However, one of

ordinary skill in the art would have no motivation to incorporate such agonist peptides into the CDR replaced antibodies disclosed to be useful as receptor inhibitory agents. Therefore, claims 1-16, 18-19, 22-23, 36, 90, and 96-99 are novel and non-obvious in view of the cited references.

With respect to claims 44-45, 85, and 87-89, Applicants respectfully submit that the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein at least a portion of a CDR region is replaced with a biologically active peptide flanked with a proline at the *carboxy terminus*. In particular, the Examiner relies on Kini et al. for the use of prolines to bracket a peptide sequence. However, Kini et al. discloses adding prolines to the ends of short peptides and does not teach adding prolines to a peptide that is inserted into the middle of a large protein such that the inserted proline has very long flanking sequences, not merely one or two amino acids added to the ends. Additionally, the results obtained by Kini et al. using the short peptides do not appear to be predictive of the results obtained when inserting a peptide into the middle of a larger protein. Kini et al. discloses that "[i]ncorporation of a proline residue on either side of RGDM enhances the potency to about the same extent" (see Kini et al. page 16, left column, first full paragraph). In contrast to the teachings of Kini et al., Applicants have found that addition of a proline residue at the carboxy terminus of a peptide which has been incorporated into a CDR region of an antibody provides superior results as compared to incorporation of a proline residue at the amino terminus of the peptide. In particular, the Table in Example 1 (see page 45 of the instant application) provides the results for various Fab clones having different residues flanking the carboxy terminus and amino terminus of the incorporated peptide as reproduced below:

Clone	**Binding Properties**	**SEQ ID NO**	**Sequence**
X1-a	Weak	25	Pro Pro (14 aa peptide) Gly Gly
X1a-11	Weak	27	Gly Gly (14 aa peptide) Gly Gly
X1a-13	Weak	29	Gly Gly (14 aa peptide) Gly Gly
X1c	Strong	31	Trp Leu (14 aa peptide) Pro Val
X2c	Weak	33	Met Ile (14 aa peptide) Val Gly
X3a	Strong	35	Val Val (14 aa peptide) Pro Val
X3b	Strong	37	Gly Pro (14 aa peptide) Pro Asp
X4b	Strong	39	Leu Pro (14 aa peptide) Pro Val
X4c	Strong	41	Ser Leu (14 aa peptide) Pro Ile

Clone	Binding Properties	SEQ ID NO	Sequence
X5a	Strong	43	Thr Met (14 aa peptide) Pro Val
X5c	Strong	45	Trp Leu (14 aa peptide) Pro Val
X7a	Weak	47	Thr Arg (14 aa peptide) Cys Ser
X7b	Weak		Deletion mutant this clone has lost the peptide
X7c	Strong	49	Gln Thr (14 aa peptide) Pro Asp

As shown in the Table above, Applicants have unexpectedly found that Fab clones having a proline residue immediately flanking the carboxy terminus of an incorporated peptide (e.g., clones X1c, X3a, X3b, X4b, X4c, X5a, X5c, and X7c) resulted in strong binders whereas Fab clones having a proline residue immediately flanking the amino terminus of an incorporated peptide did not result in strong binders (e.g., clone X1a). Based on the disclosure of Kini et al., one would have expected that the addition of a proline to the amino terminus or carboxy terminus would have produced equivalent results. Accordingly, the results obtained by Applicants for incorporation of a peptide into a CDR region are unexpected and nonobvious over the disclosure of Kini et al. relating to short peptides.

Furthermore, neither Barbas (a), Barbas (b) nor Dower make up for the deficiencies of Kini et al. In particular, Barbas (a) discloses immunoglobulins having peptide replaced CDRs and that it may be possible to optimize antibody binding by randomizing residues flanking either side, or both sides, of the incorporated peptide. However, Barbas (a) provides no teaching or suggestion that a *proline* residue flanking the *carboxy terminus* of the peptide would be useful for producing an immunoglobulin having a biologically active peptide incorporated into the CDR region. Additionally, neither Barbas (b) nor Dower suggests addition of a proline residue to the carboxy terminus of a biologically active peptide. Accordingly, no combination of the cited references teaches or suggests the unexpected and superior results obtained from inserting a *proline* residue at the *carboxy terminus* of a peptide that has been incorporated into the CDR region of an immunoglobulin molecule. Therefore, claims 44-45, 85, and 87-89, are novel and non-obvious in view of the cited references.

With respect to claim 86, Applicants respectfully submit that the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein at least a portion of a CDR region is replaced with a biologically active peptide flanked at the *carboxy terminus* with the *specifically recited amino*

acid sequences. In particular, Barbas et al. (a) teaches CDR replaced antibodies and that optimization of antibody binding may be achieved by randomizing residues flanking the incorporated peptide at either terminus. However, Barbas et al. (a) fails to teach or suggest that a dipeptide amino acid sequence should be introduced flanking the peptide, fails to teach or suggest the *specific dipeptide amino acid sequences* provided in claim 86, and fails to teach or suggest that such amino acid sequences should be incorporated at the *carboxy terminus* of the peptide introduced into the CDR region. In particular, Barbas et al. (a) teaches that the flanking regions of the peptide incorporated into the CDR region may be randomized based on the following equation: -X-$[MNN]_a$-Y-$[MNN]_b$-X-, wherein X is a trinucleotide encoding cysteine or a native amino acid residue coded by the immunoglobulin gene, N is independently any nucleotide, M is adenine (A) or cytosine (C) or analogs thereof, Y is a nucleotide sequence that encodes a minimum recognition domain of the binding site (e.g., the peptide incorporated into the CDR), and *the sum of a and b is from 5 to 50* (see e.g., page 6, lines 10-20). This equation provides an almost endless number of possible combinations of flanking residues for the incorporated polypeptide. In particular, Barbas et al. (a) teaches that the minimum number of flanking residues must be at least 5 amino acids (e.g., a + b = 5). This means that of all of the many possible combinations of flanking sequences provided in Barbas et al. (a), only a few possible permutations provide a dipeptide flanking the carboxy terminus of an incorporated peptide and these would require that the amino terminus has at least three flanking residues (e.g., a is from 3 to 48 and b is 2). Furthermore, of the few possible permutations involving a dipeptide flanking the carboxy terminus there are again many possible dipeptide combinations that would be encompassed by Barbas et al. (a), however, there is no teaching or suggestion of the particular dipeptide amino acid sequences listed in claim 86 of the instant application. Accordingly, there is no teaching or suggestion in Barbas et al. (a) for incorporation of a dipeptide amino acid sequence having any of the specific sequences recited in instant claim 86. Furthermore, Barbas et al. (b), Dower, and Kini et al. fail to make up for the deficiencies of Barbas et al. (a). In particular, none of the references teaches or suggests that the specific dipeptide amino acid sequences provided in claim 86 should be incorporated at the carboxy terminus of a biologically active peptide that has been introduced into a CDR region. Accordingly, no combination of the cited references teaches or suggests an immunoglobulin molecule, or fragment thereof, wherein at least a portion of a CDR region is replaced with a biologically

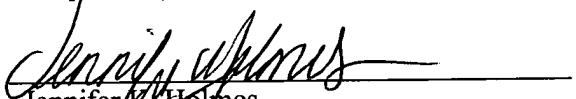
active peptide flanked at the *carboxy terminus* with the *specifically recited amino acid sequences*. Accordingly, claim 86 is novel and non-obvious in view of the cited references.

Based on the above remarks, Applicants submit that the currently claimed immunoglobulins and fragments thereof are not obvious in view of the cited references. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should any extensions of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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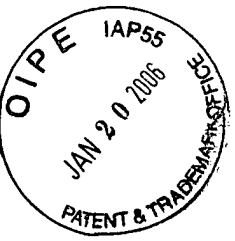

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